REMARKS/ARGUMENTS

Claims 1 and 3–10 are pending in the above-captioned application. All of these claims stand rejected. Only claim 1 is amended with this paper.

I. Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 1 and 3–10 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Claim 1 has been amended to delete the term "about." With this amendment, Applicant respectfully asserts that claim 1, as well as its dependent claims 3–10, should be found to comply with the requirements of 35 U.S.C. § 112, second paragraph.

II. Claim rejections under 35 U.S.C. § 103(a) as being unpatentable over Lipshutz et al. (US 5,856,174) in view of Chetverin et al. (US 5,616,478) and further in view of Moss et al. (US 5,135,855)

Claims 1, 3–5, and 7–10 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lipshutz et al. (US 5,856,174) in view of Chetverin et al. (US 5,616,478) and further in view of Moss et al. (US 5,135,855). This rejection is respectfully traversed. To warrant rejection under 35 U.S.C. § 103(a), all the claim limitations must be taught or suggested by the prior art. *See* MPEP § 2142.

With all due respect, it does not appear to Applicant that Lipschutz et al. teach any of the steps of Applicant's method claim 1, nor do they teach a device or system configured to carry out Applicant's claimed method.

Lipschutz et al. do not teach mixing PCR reaction components with a sieving medium, whether unpolymerized or polymerized. The only mention of a sieving medium by Lipschutz et al. is the statement in column 12, lines 31–34, that capillaries used in capillary electrophoresis methods are typically filled with an appropriate separation/sieving matrix. Lipschutz et al. state in column 11, lines 61–64, that a micro capillary array for analysis of nucleic acids is "optionally or additionally" provided for analyzing nucleic acids from the sample. I.e., such a micro capillary array is not integral to and, therefore, distinct from the

amplification chambers in which amplification of nucleic acids extracted from the sample is carried out. Thus, Lipschutz et al. are silent with regard to a sieving medium being present in their amplification chambers, which are separate structures from the micro capillary array.

Because there is no sieving medium in the amplification chambers taught by Lipschutz et al., the reference cannot teach thermocycling a PCR sieving medium in situ in the amplification chamber (i.e., in a channel) or polymerizing the sieving medium in situ after thermocycling of the sieving medium is completed.

As taught by Lipschutz et al. in column 13, lines 48–53, the various preparative (e.g., amplification) and analytical (e.g., electrophoresis) reactions are carried out in "discrete reaction, storage and/or analytical chambers disposed within a single unit or body." Because the operations are carried out in separate chambers (and optionally/additionally in microcapillary arrays in the case of electrophoresis), Lipschutz et al. do not teach separating PCR products by flowing the PCR products through a sieving medium that has been polymerized within the channel (or, in this case, chamber) in which amplification took place.

Further, because Lipschutz et al. make clear throughout the text and the figures that the various operations are carried out in separate locations (for example in column 13, lines 48–53; in column 14, lines 25–28; in column 17, lines 52–50; and particularly in Figure 3 and the text describing Figure 3 in column 17, line 61, through column 19, line 29) the systems and devices of Lipschutz et al. are not suitable for carrying out Applicant's claimed method. While structures 222–226 are not identified in the cited Lipschutz et al. reference, they fit the description of a microcapillary array given in column 11, line 66, through column 12, line 30, of the cited reference, and structure 226 is identified in a continuation (US 5,922,591) of the cited reference as representing a microcapillary electrophoresis device. Thus, Lipschutz et al. make clear that amplification and electrophoresis cannot be carried out in the same location.

The Examiner cites Chevretin et al. as providing a supportive disclosure that teaches amplification of nucleic acids within an unpolymerized sieving media. Chevretin et al. do not, however, teach amplifying nucleic acids within an unpolymerized sieving medium and then polymerizing the sieving medium prior to electrophoretically separating the amplification product in the same sieving medium. In fact, Chevretin et al. teach away from doing so.

Chevretin et al. focus on "growing" nucleic acid "colonies" in an immobilized medium, e.g., a polymerized medium. The method is similar to the time-honored laboratory technique of growing clumps of microbes on a medium in a Petri dish and identifying the microbes based on characteristics of the individual clumps. Chevretin et al. emphasize throughout the patent that the value of their method lies in the fact that each colony resides within a limited zone, with each colony comprising individual clones. "[D]ifferent colonies occupy separate zones within the immobilized medium, and this allows the respective clones to be observed and handled separately." Column 5, lines 2–5. The point of using a solid matrix (e.g., a polymerized medium) is to "retard the spreading of the colonies caused by diffusion and thus increase the resolving power of the method, especially when amplifying small nucleic acids." Column 5, lines 33–35. Thus, the method involves identifying amplification products by their locations within a solid medium, eliminating any need for electrophoresis or other analysis methods. Subjecting the media containing amplification products taught by Chevretin et al. to electrophoretic separation would defeat the purpose of the invention.

Chevretin et al. specifically teach away from conducting amplification in an unpolymerized medium. "It is preferred to suppress the reaction until the medium gets immobilized, especially in the case of an amplification reaction; otherwise the reaction products will be prematurely synthesized and spread throughout the medium." Column 8, lines 48–51. "Expression of nucleic acids for screening purposes can be done in a liquid reaction medium, but preferably it is carried out in an immobilized medium shaped into at least one thin layer according to our invention." Column 13, line 66, through column 14, line 2.

As the Examiner points out, Chevretin et al. suggest the use of an uncast medium for cDNA synthesis steps, presumably because RNA is more sensitive to the temperatures required for casting than is DNA; but this is an exception to the teachings of Chevretin et al. While Chevretin et al. are vague with regard to this step, cDNA synthesis is presumably a sample preparation step, and amplification is then carried out on the resulting cDNA in the cast gel to allow differentiation of the amplification products. Therefore, suggesting that cDNA synthesis be carried out in an uncast medium would not provide motivation for performing amplification for the purpose of separation and identification in an uncast medium.

The Examiner states that Chevretin et al. teach in column 12, lines 30–40, that sieving mediums may be impregnated with amplification enzymes before casting to prevent problems due to harsh polymerization conditions. Applicant must respectfully disagree. In the cited text, Chevretin et al. teach, "Impregnation of pre-cast gels with enzymes and/or substrates can be a choice when the conditions of gel preparation are too strong for these labile biological substances." It appears to Applicant that Chevretin et al. are suggesting first casting the gels and then impregnating the cast gels with components sensitive to polymerization conditions. Applicant's interpretation of the term "pre-cast" is supported by column 12, lines 55–62, in which Chevretin et al. suggest pre-forming (i.e., pre-casting) an agarose gel layer and then soaking it in a solution containing enzymes and/or substrates. Chevretin et al. state, "Similarly, polyacrylamide or polyacrylamide:agarose gels can also be pre-cast, washed, and then impregnated with enzyme(s) and or substrates."

The Examiner cites Moss et al. as teaching a nucleic acid separation electrophoresis procedure using a medium having a polymer concentration that is less than 0.4%. The Examiner specifically cites column 4, lines 25–40. Applicant points out that Moss et al. teach "a 0.4% polyacrylamide-urea gel" within the cited text. This is not a polymer concentration that is less than 0.4%. Applicant has limited claim 1 to a polymer concentration less than 0.4%. Moss et al. do not teach a polymer concentration that meets this limitation.

Therefore, the combination cited by the Examiner does not teach or suggest all of the limitations of currently amended claim 1. Withdrawal of the rejection of claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Lipshutz et al. (US 5,856,174) in view of Chetverin et al. (US 5,616,478) and further in view of Moss et al. (US 5,135,855) is respectfully requested.

Claims 3–5 and 7–10 depend directly or indirectly from claim 1. Any claim depending from a nonobvious claim is also nonobvious. *See* MPEP § 2143.03 and *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Therefore, dependent claims 3–5 and 7–10 are nonobvious. Withdrawal of the rejection of these claims as unpatentable over Lipshutz et al. in view of Chetverin et al. and further in view of Moss et al. is also respectfully requested.

III. Claim rejection under 35 U.S.C. § 103(a) as being unpatentable over Lipshutz et al. (US 5,856,174) in view of Chetverin et al. (US 5,616,478) and further in view of Mitra et al. ("In situ localized amplification and contact replication ...") and Dubrow (US 5,164,055)

Claim 6 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lipshutz et al. (US 5,856,174) in view of Chetverin et al. (US 5,616,478) and further in view of Mitra et al., "In situ localized amplification and contact replication of many individual DNA molecules," Nucleic Acids Res. 1999 Dec 15;27(24):e34), as applied to claims 1, 3–5, and 7–10, and further in view of Dubrow (US 5,164,055). The rejection is respectfully traversed.

As demonstrated above, Applicant's currently amended claim 1 is nonobvious. Claim 6 depends directly from claim 1. As any claim depending from a nonobvious claim is also nonobvious, dependent claim 6 is nonobvious. Withdrawal of the rejection of claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Lipshutz et al. in view of Chetverin et al. and further in view of Mitra et al. and Dubrow is, therefore, respectfully requested.

Conclusion

For the foregoing reasons, Applicant believes all the pending claims are in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned attorney.

Respectfully submitted,

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